REMARKS

These remarks are in response to the Office Action mailed June 27, 2006 ("the Office Action"). Claims 1, 5, 6-13, 16, 18-25, and 28 have been amended. Claims 1, 13, and 25 have been amended to delete the term "preptin agonist." They further incorporate limitations from dependent claims. More specifically, claim 1 incorporates limitations from claims 3 and 5, claim 13 incorporates limitations from claims 15 and 17, and claim 25 incorporates limitations from claims 27 and 29. Additional support for these amendments is found, e.g., in paragraphs [0007]-[0025] of the specification (paragraph numbers refer to the specification as published under U.S. Patent Publication No. 2006/0116318). Claims 6-12, 18-24, and 30-36 have been amended to delete the term "preptin agonist" and replace it with "peptide" so as to properly refer to the "peptide" recited in preceding claims. Claims 6-8, 16 and 17-20 have been amended to depend from pending claims, rather than from preceding claims that have been canceled. Claims 3, 5, 15, 17, 27, 29, 37, and 38 have been canceled. No new matter has been added. Claims 1, 2, 4, 6-14, 16, 18-26, and 28 are under examination.

Reconsideration of the claims, as amended, is respectfully requested in view of the following remarks.

Rejection of claims 1- 38 under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-38 were rejected as lacking written description. The Office Action stated:

> The specification discloses the complete structure of the preptin analogues of Formula (I) however evidence that these peptides are effective at promoting bone cell growth is provided only for rat and human preptin (SEQ ID NOs: 2 and 3, respectively). The specification does not provide the complete or partial [*sic*] of a single additional species that meets the functional limitations of the claimed invention…In addition, the specification fails to describe the physical and chemical properties that are essential for active forms of preptin and its analogues or agonists. Data is not presented in the specification or in the prior art that identifies the residues or chemical groups that give rise to receptor binding and activation. Likewise, the structural requirements for the claimed function are not disclosed. Finally, the application does not describe an assay for identifying additional active compounds or a means to predict which species would be effective (pages 2-3).

This is respectfully traversed. The claims, as amended, are directed to methods for treating bone conditions, maintaining bone density, and stimulating osteoblast growth or modulating osteoblast apoptosis using preptin, a preptin analog, or a peptide including an amino acid sequence that is at least 60% identical to SEQ ID NO: 1, 2, or 3, or a fragment thereof, wherein the peptide promotes osteoblast proliferation. The Office Action acknowledged that the description requirement is met for uses of rat and human preptin (SEQ ID NOs:2 and 3).

Regarding the recitation of "preptin" in the claims, the specification defines preptin as an isolated peptide of 34 amino acids, the sequence of which is described in formula (I)(paragraphs [0007]-[00017]). The Office Action noted that the specification discloses the *complete structure* of the peptides of formula (I) but found it lacking written description because "evidence that these peptides are effective at promoting bone cell growth is provided only for rat and human preptin." The specification provides assays for determining whether a peptide possesses biological activity. See, for example, the osteoblast proliferation assay described in Example 1. One may employ this assay to evaluate activity of various peptides. In any event, the demonstration in the specification that different species possess biological activity coupled with disclosure of the complete structure of peptides in the genus satisfies the written description requirement. Reduction to practice and disclosure of structure allow the skilled artisan to recognize that Applicants were in possession of the genus encompassed by this limitation.

The sufficiency of written description support for this limitation is further illustrated by the analysis in Example 14 of the Revised Interim Written Description Guidelines Training Materials ("the Guidelines"). This Example describes a hypothetical scenario in which a protein having at least 95% identity to a reference sequence, and a specific functional activity, is claimed. The Guidelines affirm the adequacy of the written description for this claim, even though only a single representative species is disclosed and even though the full structure of the genus is not disclosed. The Guidelines state that the disclosure of a single protein species is sufficiently representative of the claimed genus in part because the Applicant provided an assay with which to assay activity. The preptin species recited in the claims are supported to an even greater extent, given the reduction to practice of multiple species and disclosure of structure of

the entire genus. Thus, the preptin species encompassed by the claims fulfill the criteria of Example 14 and meet the requirement for written description.

The Office Action stated that description was not met for uses of preptin analogs and agonists. Preptin analogs include functional equivalents of preptin that are immunologically cross-reactive with and have substantially the same function as preptin (specification, paragraph [0021]). Examples of analogs include fragments of preptin containing 6-33 amino acids, and peptides that include substitutions. The term "preptin agonists" no longer appears in the claims. The claims instead refer to peptides that include a sequence at least 60% identical to SEQ ID NO:1, 2, or 3, or a fragment thereof, wherein the peptide promotes osteoblast proliferation.

Description for preptin analogs and the recited peptides is provided in the specification. It was asserted that the specification does not provide the complete or partial structure of a single additional species that meets the functional limitations of the claimed invention. Applicants note that the specification provide numerous examples of compounds that are analogs or fragments. The specification describes peptides including preptin fragments of particular lengths (e.g. 6-33 amino acids of a full-length preptin; peptides containing 17-33 amino acids of SEQ ID NO:3; peptides containing residues 17-34 of SEQ ID NO:3). The analogs and peptides posses specific structural features (immunological cross-reactivity with preptin, identity to specific sequences) and functional features (promotion of osteoblast proliferation).

It was alleged that "[w]ith respect to agonists, which are described as those compounds exhibiting a tight binding affinity to the preptin receptor, the identity of the receptor is not known. Thus, it is not possible to measure the affinity of a potential agonist to determine if it meets the definition of agonist outlined in the specification." The claims, as amended, recite analogs and peptides that possess a specified degree of identity to a reference sequence and a functional activity. Therefore, this point is inapplicable to the claims.

It was alleged that the application does not describe an assay for identifying additional active compounds or a means to predict which species would be effective. This is incorrect. Example 1 describes an assay for evaluating osteoblast proliferation in the presence of preptin. Example 2 describes an assay for evaluating apoptosis and phosphorylation of signaling proteins in cells treated with preptin. Example 3 describes an *in vivo* assay for testing the effects of

preptin administered to animals. All of these assays are suitable for testing compounds. The specification also cites references that provide useful assay methods (see, e.g., paragraph [0051]). Support for assays is provided in the present case. In view of the foregoing, withdrawal of this rejection is respectfully requested.

Rejection of claims 1- 38 under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-38 were rejected as lacking enablement. The Office Action stated that uses of rat and human preptin are enabled, but that enablement for all other preptins, preptin analogs, or preptin agonists is lacking. Applicants respectfully traverse the rejection.

The claims are drawn to methods for treating bone conditions, maintaining bone density, and stimulating osteoblast growth or modulating osteoblast apoptosis using preptin, a preptin analog, or a peptide including an amino acid sequence that is at least 60% identical to SEQ ID NO: 1, 2, or 3, or a fragment thereof, wherein the peptide promotes osteoblast proliferation. Working examples in the specification show, *inter alia*, that preptin stimulates osteoblast proliferation, induces phosphorylation of p42/p44 MAP kinases, and promotes bone growth *in vivo*. Analogs and peptides encompassed by the claims share structural and functional features with these forms of preptin.

The Office Action discussed the factors set forth in *In re Wands* (858 F.2d 731 (Fed. Cir. 1988)) with respect to enablement of the claims. Regarding predictability of the art, the Office Action stated that "[t]he ability to predict whether or not a particular analogue or agonist of preptin is active depends on the ability to predict the structure of the peptide, the ability to predict the interaction of the peptide and receptor, and the ability to predict whether or not a given interaction will succeed in activating this receptor…[T]he state of the art, though advanced in recent years, is not at a level to provide the detailed atomic-resolution information necessary to predict ligand-receptor interactions" (page 6).

Applicants disagree that the structures of analogs need to be resolved at atomic resolution in order to determine their activity. The assays in the specification show that activity can be measured without first solving the structure of molecules involved. The Office Action cited Ginalski et al. (*Nuc. Acids Res.*, 33:1874, 2005) as evidence of the difficulties of structure

prediction. A reliable method for three-dimensional structure prediction would be a powerful tool for rational drug design. However, the claims do not require structure prediction. One may synthesize and test the claimed preptin, preptin analogs, and peptides without a structure in hand.

The Office Action urged that even when a structure is known and its activity is well-established, it is difficult to predict the effect of individual substitutions or deletions. There is no requirement for one skilled in the art to predict *a priori* the significance of every amino acid in a polypeptide. It was a routine matter to generate and analyze preptin, preptin analogs, and peptides at the time the present application was filed, and it is agreed that the level of skill in the art is high (Office Action, page 6).

Regarding the breadth of the claims, Applicants note that the breadth of the claims has been narrowed to recite peptides with particular features rather than agonists.

As to the amount of direction or guidance presented, and the presence of working examples, the Office Action stated that "the specification provides only limited working examples…The specification does not provide an assay for identifying potentially active compounds from the vast number of claimed species or a means to predict which species would be effective" (page 9). Applicants provide numerous *in vitro* and *in vivo* methods for assaying preptin compositions. These assays are in no way "limited" and there is no basis for questioning their usefulness in evaluating activity of preptin, preptin analog, and peptide compositions. Of note, As the Examiner knows, the test for undue experimentation is not merely quantitative. Even a considerable amount of experimentation is permissible if it is merely routine *or* if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP at 2164.06 citing *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489 (CCPA 1976)). Screening an analog or peptide to practice the claimed method would be routine in view of the guidance provided in the specification and the teachings of the art. The experimentation required to show that other untested species are also effective is not undue.

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

Rejection of claims 1- 38 under 35 U.S.C. § 112, second paragraph

Claims 1, 3-13, 15-25, and 27-38 were rejected as indefinite for including the term "preptin agonist." The claims, as amended, do not use this term. Therefore, the ground for rejection does not apply. Withdrawal of the rejection is requested.

Rejection of claims 37 and 38 under 35 U.S.C. § 103

Claims 37 and 38 were rejected as unpatentable over Cooper et al. (WO 99/78805). Claims 37 and 38 have been canceled in the present amendment. This rejection may be withdrawn.

CONCLUSION

Allowance of the claims is respectfully requested in view of the above remarks. A Petition for Three-Month Extension of Time and the associated fee is being filed concurrently with this Amendment in Reply. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 11752-010US1.

Respectfully submitted,

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